



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

⑪ Publication number:

0 181 525  
A2

⑫

## EUROPEAN PATENT APPLICATION

⑬ Application number: 85113257.1

⑮ Int. Cl.4: A 61 K 31/425

⑭ Date of filing: 18.10.85

A 61 K 9/18, A 61 K 47/00

⑯ Priority: 13.11.84 US 670839

⑰ Applicant: AMERICAN CYANAMID COMPANY  
1937 West Main Street P.O. Box 60  
Stamford Connecticut 06904(US)

⑯ Date of publication of application:  
21.05.86 Bulletin 86/21

⑱ Inventor: Quinlan, James Michael  
135 Edinburg Road  
Trenton New Jersey 08619(US)

⑰ Designated Contracting States:  
AT BE CH DE FR GB IT LI NL SE

⑲ Representative: Wächtershäuser, Günter, Dr.  
Tal 29  
D-8000 München 2(DE)

⑳ Anthelmintic paste compositions containing resinates of D1-6-phenyl-2,3,5,6-tetrahydroimidazo(2,1-b)thiazole.

㉑ The invention provides physically stable anthelmintic  
paste compositions containing resinates of dl-6-phenyl-  
2,3,5,6-tetrahydroimidazo[2,1-b]thiazole and a wide variety  
of therapeutic agents such as antibiotics, vitamins, vaccines,  
mineral supplements and/or other anthelmintic compounds.

EP 0 181 525 A2

29,736

-1-

ANTHELMINTIC PASTE COMPOSITIONS  
CONTAINING RESINATES OF DI-6-PHENYL-2,3,5,6-  
TETRAHYDROIMIDAZO[2,1-b]THIAZOLE

SUMMARY OF THE INVENTION

5 The desirability of paste compositions for the oral administration of anthelmintic compositions is described in United States Patent No 3,746,490. The patent describes pastes of liquid dimethyl-2,2-dichloro-vinyl phosphate (or DDVP) alone and contained in a  
10 polyvinyl chloride pellets.

Other anthelmintic paste compositions are described in United States Patent No 4,141,975, which describes an anthelmintic paste composition containing 0,0-dimethyl 1-hydroxy-2,2,2-trichloroethylphosphonate (Trichlorfon), and United States Patent No 4,277,467 which describes anthelmintic paste compositions containing trichlorfon and N-(2-methoxyacetamide-4-phenyl-thiophenyl)-N',N"-bis-methoxycarbonylquanidine (Febantel).  
15

20 The use of 1-6-phenyl-2,3,5,6-tetrahydro-imidazo[2,1-b]thiazole hydrochloride and trichlorfon, as a combination anthelmintic treatment, suitable for oral or parenteral administration is described in United States Patent No 3,937,825.

5 Previous attempts to prepare anthelmintic  
paste compositions containing two active ingredients  
such as the hydrochloride salt of dl-6-phenyl-2,3,5,6-  
tetrahydroimidazo[2,1-b]-thiazole or l-6-phenyl-2,3,5,6-  
10 tetrahydroimidazo[2,1-b]thiazole, hereinafter referred  
to respectively as dl-tetramisole and l-tetramisole,  
with organophosphate anthelmintics such as trichlorfon,  
famphur, coumaphos, dimethoate, cythioate, chlorpyrifos,  
15 temephos and the like, resulted in paste compositions  
which exhibit physical instability overtime and at  
elevated temperatures. These pastes shrink and separate  
upon aging and at elevated temperatures, giving compo-  
sitions which are non-homogeneous and unsuitable for  
use.

15 It has been found that physically stable  
anthelmintic paste compositions containing dl-tetra-  
misole and l-tetramisole in combinations with other  
anthelmintics such as the organophosphate compounds  
described above may be prepared when resinated dl- or  
20 l-tetramisole is used to prepare the anthelmintic com-  
bination pastes. The resulting paste compositions  
comprising 2% to 24% on a weight basis of dl- or  
l-tetramisole resinate, 40% to 75% on a weight basis of  
heavy mineral oil, 0.0% to 2.5% on a weight basis of a  
25 nonionic surfactant, 0.0% to 31% on a weight basis of  
an organophosphate, 0.0% to 5.0% on a weight basis of  
barium sulfate, 2.0% to 10.0% on a weight basis of a  
fumed or precipitated silica, exhibit greatly improved  
30 physical stability over extended periods of time and at  
elevated temperatures in comparison to paste composi-  
tions prepared using acid salts such as the hydro-  
chloride salt of dl- or l-tetramisole.

-3-

Resinated forms of dl-tetramisole and l-tetramisole suitable for use in preparing paste compositions of the invention are described in United States Patent No 3,574,227. United States Patent No 3,574,227 addresses 5 the problems associated with the bitter taste of these anthelmintics and their chemical instability which can result in chemical degradation and loss of potency when combined in animal feedstuffs. It has been found that resinated forms of dl-tetramisole and l-tetramisole may 10 be used to prepare physically stable paste compositions containing other active ingredients such as the organo-phosphate compounds described above which are not compatible with the acid addition salts of dl-tetramisole and l-tetramisole.

15 Strongly acidic resins are preferred in the invention compositions since they provide resinates in which the tetramisole is more strongly ionically bonded to the ion exchanged resin, thus substantially preventing ionization of the tetramisole. The preferred resins 20 for the manufacture of the resinates of the invention are the strongly acidic resins including sulfonated polystyrenes prepared from styrene and from about 1 to about 20 weight percent of divinyl benzene which functions as a cross-linking agent. Examples of resins 25 useful in the invention include AMBERLITE® IR-120 and IR-112, and DOWEX® 50 and 50W resins; sulfonated phenolic resins including AMBERLITE® IR-1 resins; cellulose alkylsulfonic acid resins including Cellex SE resin; phenol methylene sulfonic acid resins including 30 Acirolite C-131 resin; and sulfonated coal.

Cythioate phenyl O,O-dimethyl O-p-sulfamoyl phosphorothioate

5 Chlorpyrifos 0,O-diethyl O-(3,5,6-trichloro-2-pyridyl)-phosphorothioate

Temephos O,O'-(thiodi-4,1-phenylene)bis(O,O-dimethyl phosphorthioate

EXAMPLE 1

10 Polysorbate 20 60 g, 1.50% on a weight basis is added to heavy mineral oil 2164.64 g, 53.12% on a weight basis and the resulting mixture agitated in a Ross double planetary mixer for five minutes. 1-Tetramisole resinate 460 g, 11.50 on a weight basis is then added, after mixing for five minutes, a preblend, 1226 g, 30.65% on a weight basis, comprised of mixture of technical trichlorfon (96.2% pure) 97.5% by weight and fumed silica, 2.5% by weight which has been milled to a mean particle size of 62 microns is added. After

15 blending for ten minutes fumed silica 3.23% on a weight basis is added and blending continued for 15 minutes. The resulting mixture is homogenized in a Homomixer, yielding the desired anthelmintic paste combination composition.

20 25 By utilizing the above procedure and substituting the appropriate components, the paste compositions summarized in Table I below may be prepared.

30

35

TABLE I

| Composition of<br>1-tetramisole | 1              | 2              | 3                | 4                 | 5                | 6                | 7                | 8                | 9                | 10               |
|---------------------------------|----------------|----------------|------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Component                       | % w/w          | % w/w          | % w/w            | % w/w             | % w/w            | % w/w            | % w/w            | % w/w            | % w/w            | % w/w            |
| HCl                             | 5.83<br>(5.75) | 5.83<br>(5.75) | 12.28<br>(11.72) | -                 | -                | -                | -                | -                | -                | -                |
| Resinate                        | -              | -              | -                | 12.00*<br>(5.75)  | 12.0<br>(5.75)   | 12.0<br>(5.75)   | 12.0<br>(5.75)   | 11.50<br>(5.75)  | 11.50<br>(5.75)  | 11.50<br>(5.75)  |
| Famphur                         | 29.06          | -              | -                | -                 | 29.2*<br>(28.47) | 29.2*<br>(28.47) | 29.2*<br>(28.47) | -                | -                | -                |
| Trichlorfon                     | -              | 29.06          | -                | 30.00*<br>(28.75) | -                | -                | -                | 30.65*<br>(40.0) | 30.81*<br>(30.0) | 30.81*<br>(30.0) |
| Polyisorbate 20                 | 1.0            | 1.0            | 1.01             | 1.50              | 0.7              | 1.10             | 1.50             | 1.50             | 1.50             | 1.50             |
| Colloidal silica                | 2.75           | 2.75           | 3.55             | 2.90              | 3.00             | 2.75             | 2.75             | 3.23             | 3.23             | 3.23             |
| BaSO <sub>4</sub>               | 5.00           | 5.00           | 10.15            | 5.00              | 5.00             | 5.00             | 5.00             | -                | -                | -                |
| Heavy mineral oil               | 56.36          | 56.36          | 72.99            | 48.6              | 50.1             | 49.95            | 49.55            | 53.116           | 52.96            | 52.96            |

\*Premix containing 1% to 3% by weight of fumed silica from milling.

( ) Denotes % active ingredient, figuring for 1-tetramisole expressed as HCl equivalent.

EXAMPLE 2Physical stability of anthelmintic paste compositions

5 The physical stability of the anthelmintic paste compositions of the invention is evaluated by storing samples at 37°C and 45°C and visually inspecting the paste periodically for shrinkage or clear liquid formation.

10 The results of these experiments summarized in Table II below demonstrate the enhanced physical stability of anthelmintic paste compositions containing resinated 1-tetramisole and organophosphate compounds compared to the control combinations which are prepared using the hydrochloride salt.

15

20

25

30

35

TABLE II  
Stability of paste compositions

| Composition of |          | 1         | 2         | 3     | 4     | 5      | 6      | 7      | 8      | 9      | 10     |
|----------------|----------|-----------|-----------|-------|-------|--------|--------|--------|--------|--------|--------|
| Stability      |          | % w/w     | % w/w     | % w/w | % w/w | % w/w  | % w/w  | % w/w  | % w/w  | % w/w  | % w/w  |
| 37°C           | 2 months | Separates | Separates |       |       |        |        |        |        |        |        |
|                | 3 months |           |           |       |       |        |        |        |        |        |        |
| 45°C           | 6 months |           |           |       |       |        | Stable | Stable | Stable | Stable | Stable |
|                | 1 months | Separates | Separates |       |       |        |        |        |        |        |        |
|                | 2 months |           |           |       |       | Stable |        |        |        |        |        |
|                | 6 months |           |           |       |       |        | Stable | Stable | Stable | Stable | Stable |

29,736

-10-

## WHAT IS CLAIMED IS:

1. A physically stable anthelmintic paste composition comprising 2% to 24% on a weight basis of resinated l-tetramisole or resinated dl-tetramisole, 40% to 75% on a weight basis of heavy mineral oil, 0.0% to 2.5% on a weight basis of a nonionic surfactant, 0.0% to 31.0% of a second active ingredient of an organophosphate compound, antibiotic, vaccine, vitamins or mineral supplement, 0% to 5% on a weight basis of an agent to increase the density of the composition such as barium sulfate, and 2% to 10% on a weight of a fumed or precipitated silica.
2. A composition according to Claim 1, wherein the second active ingredient is an organophosphate compound selected from famphur, trichlorfon, coumaphos, dimethoate, cythioate, chlorpyrifos, or temephos.
3. A composition according to Claim 2, wherein the second active ingredient is trichlorfon.
4. A composition according to Claim 2, wherein the second active ingredient is famphur.
5. A composition according to Claim 2, containing 2% to 24% on a weight basis of resinated l-tetramisole and 2% to 31% on a weight basis of trichlorfon.
6. A composition according to Claim 2, containing 2% to 24% on a weight basis of resinated l-tetramisole and 2% to 31% on a weight basis of famphur.

7. A composition according to Claim 1, wherein the second active ingredient is an antibiotic of chlorotetracycline, sulfamethazine, sulfethoxypyridazine, sulfathiazole, tylosin or nitrofuran.

8. A composition according to Claim 1, wherein the second active ingredient is a vaccine.

9. A composition according to Claim 1, wherein the second active ingredient is a vitamin and/or a mineral supplement.